

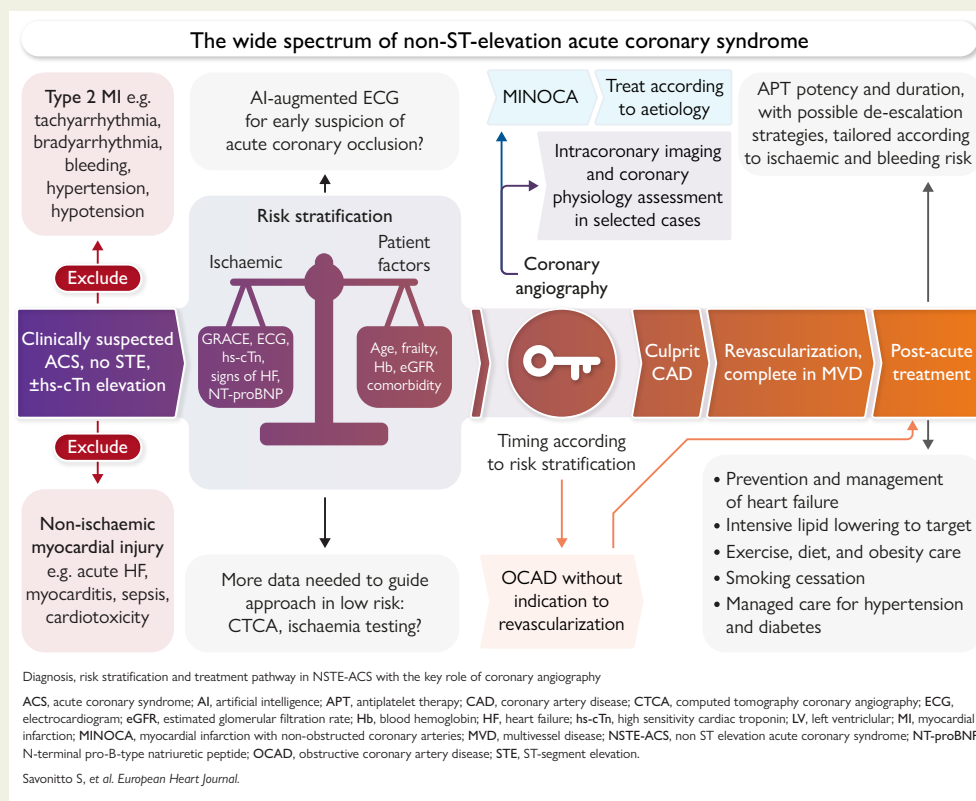
Non-ST-segment elevation acute coronary syndrome: understanding the full spectrum to guide management

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Graphical Abstract



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Diagnosis, risk stratification, and treatment pathway in NSTE-ACS with the key role of coronary angiography. AI, artificial intelligence; APT, antiplatelet therapy; CAD, coronary artery disease; CTCA: computed tomography coronary angiography; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; LV, left ventricular; MI, myocardial infarction; MINOCAs, myocardial infarction with non-obstructed coronary arteries; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OCAD, obstructive coronary artery disease; STE, ST-segment elevation.

Abstract

Acute coronary syndromes are caused by obstructive coronary thrombosis complicating myocardial ischaemic disease and are dichotomously classified according to their electrocardiographic presentation as ST-segment elevation myocardial infarction or non-ST-segment elevation acute coronary syndrome, either without or with elevated myocardial necrosis markers. Initial diagnosis and risk stratification are reliably guided by symptoms, electrocardiographic changes, and troponin elevation and require exclusion of alternative conditions, such as Type 2 myocardial infarction and myocardial injury due to systemic conditions. Timely coronary angiography is a key component of the initial diagnosis to assess the presence of occlusive coronary artery disease, rather than an myocardial infarction with non-occluded coronary arteries, and the suitability for revascularization. While clinical trials with randomization prior to angiography have shown reduction in recurrent myocardial infarction and urgent revascularization with a neutral effect on mortality from an early invasive approach, increased revascularization rates have been systematically associated with reduced mortality in registries and administrative databases. Complete revascularization in patients with multivessel disease has been shown to reduce mortality compared with culprit-only revascularization. The safety of this approach has been shown even in fragile, elderly, and multimorbid patients. Post-acute treatment should be focused on patient-tailored antithrombotic therapy and disease-modifying secondary prevention approaches. This review describes the complex spectrum of non-ST-segment elevation acute coronary syndrome and the importance of complete clinical and coronary angiographic assessment for optimal patient-centred treatment.

Keywords

Non-ST-segment elevation acute coronary syndrome • Myocardial infarction • Coronary angiography • Coronary revascularization

Background

Acute coronary syndromes (ACSs), including myocardial infarction (MI), unstable angina (UA), and ischaemic sudden death,¹ are usually caused by a rapid reduction of blood supply to the myocardium due to coronary obstruction. In many instances, an ACS is the first clinical manifestation of atherosclerotic coronary artery disease (CAD)² in previously asymptomatic patients. A recent evolution in nomenclature has encompassed chronic and acute disease under the name of 'myocardial ischaemic syndromes'.³ Early detection, prevention, and management of atherosclerosis should inform future research and health policy to reduce ACS incidence and specific mortality,² but other mechanisms, including microvascular dysfunction, coronary spasm, spontaneous coronary artery dissection, calcific nodules, and embolism, can also cause ACS with variations according to sex and age.⁴ These alternative mechanisms are more frequent in non-ST-segment elevation ACS (NSTE-ACS), as compared with ST-segment elevation MI (STEMI).

The epidemiology of ACS has recently evolved with an overall reduction in incidence due to control of traditional cardiovascular risk factors,⁵ but a recognized growing impact of pollution and climate change, which have been shown to worsen atherosclerosis and precipitate ACS and stroke.^{6–10}

The treatment of ACS depends on electrocardiographic (ECG) presentation indicating coronary artery occlusion and extent of myocardial ischaemia. In the case of STEMI, almost always due to an acute thrombotic occlusion of a major coronary artery, prompt reperfusion using thrombolysis or percutaneous coronary intervention (PCI), based on solid evidence from randomized clinical trials (RCTs), has led to a dramatic reduction in mortality with the implementation of regional networks.^{11–14} However, the situation is more complex in NSTE-ACS, due to less univocal pathophysiologic mechanisms, overlap with

Type 2 MI (T2MI),¹⁵ MI with non-obstructed coronary arteries (MINOCAs),^{16,17} differential diagnosis of Takotsubo syndrome^{18,19} or myocarditis, evolving diagnostic tools and pharmacologic approaches, and uncertain evidence concerning the role and timing of coronary intervention.

Compared with STEMI, NSTE-ACS patients are older, with higher prevalence of prior MI, coronary revascularizations, and comorbidities.^{20–22} Randomized clinical trials investigating the effect of a systematic invasive approach in NSTE-ACS have failed to show lower mortality, as compared with a more conservative approach. Nevertheless, since more than a decade, practice guidelines have recommended an invasive approach in the great majority of cases, and data from several national registries have shown improvement in outcomes, including mortality, associated with increasing rates of early revascularization.^{23–27} The present article reviews the clinical complexity of NSTE-ACS, the epidemiologic impact of high-sensitivity diagnostic assays, the need to complete patient assessment with coronary angiography (CAG) and other imaging techniques, the impact of early revascularization, and growing evidence about a patient-tailored approach to long-term treatment.

Demographics and sex differences in non-ST-segment elevation myocardial infarction

Non-ST-segment elevation myocardial infarction occurs more frequently than STEMI in older adults, possibly as a result of long-standing CAD with well-developed collateral circulation.²⁸ Given the current trend to advanced life expectancy, it is likely that the incidence of NSTEMI will continue to increase, particularly in upper-middle- and

Table 1 Braunwald's classification of unstable angina⁴³

Severity	Clinical circumstances		
	A. Develops in the presence of extracardiac condition that intensifies myocardial ischaemia (secondary UA)	B. Develops in the absence of extracardiac condition (primary UA)	C. Develops within 2 weeks after AMI
I. New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II. Angina at rest within past month but not within preceding 48 h (angina at rest, subacute)	IIA	IIB	IIC
III. Angina at rest within 48 h (angina at rest, acute)	IIIA	IIIB	IIIC
Comments	These categories may apply to patients with CAD but, as for Type 2 MI, should not be classified as ACS	These categories apply to patients without or with known CAD, e.g. with prior MI, PCI, or CABG. Incidence of 'unstable angina' reduced after introduction of hs-cTn assays: more cases with final diagnosis of AMI	These categories are now reduced with the almost systematic use of complete revascularization, but may occur in cases treated conservatively

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; hs-cTn, high-sensitivity troponin; UA, unstable angina.

lower-middle-income regions of the world.² Older adults with NSTE-ACS had been traditionally underrepresented in clinical trials,²⁹ but dedicated studies have been carried out since 2007 investigating the effect of an invasive approach and dedicated drug therapy.³⁰ On the other hand, about 5%–7% of NSTE-ACS occur in patients ≤45 years, particularly in low- to lower-middle-income countries.³¹ Family history of young MI and smoking are the dominant risk factors, but also dyslipidaemia and obesity increasingly play a key role in young NSTE-ACS patients.^{32–36}

Women are older than men at the time of presentation, with more comorbid conditions such as hypertension, diabetes, and renal insufficiency. On average, they have less extensive CAD than age-matched men³⁷ and are less likely to receive CAG and revascularization, even when clinically indicated.³⁸ The lower use of invasive therapy may contribute to the higher short-term mortality compared with men. However, when mortality rates are adjusted for comorbidities and therapy, long-term outcomes are comparable or even slightly better in women.^{39,40}

Racial and ethnic disparities are present in particular in the US NSTEMI population. African American and Hispanic patients are less likely to receive evidence-based therapies and timely intervention and suffer higher mortality compared with whites. This disparity reflects systemic barriers to care rather than biological differences.⁴¹

Clinical manifestations

As compared with chronic coronary syndrome,⁴² ACS patients have more than a 10-fold increase in first-year mortality rate (from 0.6% per year to 5%–10%) in survivors of the acute phase. The

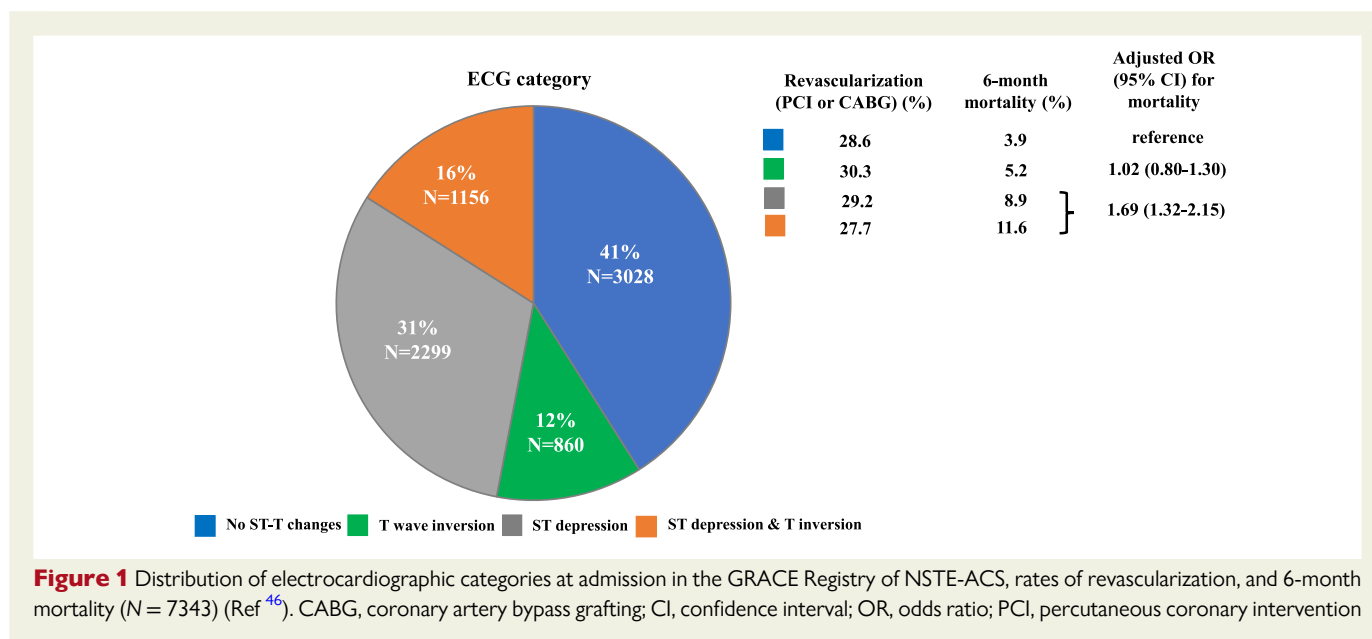
characteristics of ischaemic symptoms, ECG presentation, and extent of elevation of myocardial necrosis markers have been shown to possess both diagnostic and prognostic values.

Ischaemic symptoms

A key point in defining ACS is the sudden, and/or rapidly progressive, development of severe symptoms of myocardial ischaemia often without obvious provoking factors. In 1989, Braunwald classified UA based on the severity of symptoms, the presumed precipitating cause, and the ECG changes, with the intent to categorize the various clinical presentations while seeking tailored treatment prior to obtaining biomarker results (Table 1).⁴³ Although this classification may be associated with variable coronary characteristics,⁴⁴ it continues to be of value in initial assessment. However, the development of high-sensitivity cardiac troponin (hs-cTn) assays has markedly reduced the percentage of patients finally classified as UA as compared with NSTEMI.^{1,45} Symptoms and signs of heart failure (HF) and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are also of critical importance for the initial diagnosis, risk stratification, and the institution of immediate therapy.^{46–48} Baseline serum creatinine and blood haemoglobin levels have therapeutic and prognostic implications.^{49–53} Older age, cardiovascular risk factors, prior cardiovascular events, and current therapy assist in shaping the diagnosis.

Diagnostic and prognostic value of the electrocardiogram

The 12-lead ECG is central to each stage of ACS management including diagnosis, prognosis, clinical decision, and monitoring therapy.⁵⁴ About



40% of NSTEMI-ACS patients present without ischaemic ECG changes, 30% with ST-segment depression, and about 30% with T wave changes alone or accompanied with ST depression (Figure 1).⁴⁶ A small minority present with transient (<30 min) STE. Since qualifying symptoms may have waned at the time of first medical contact, it is important to obtain serial ECGs, particularly if recurrent symptoms develop, since subsequent ECGs often disclose dynamic diagnostic information such as transient STE or depression.¹²

Patients with a normal ECG are at lower risk for complications.^{55,56} In the Global Registry of Acute Coronary Events (GRACE) including 7343 NSTEMI-ACS patients, ST depression on the admission ECG was an independent predictor of 6-month mortality together with older age, elevated cardiac biomarkers, Killip class, cardiac arrest, and serum creatinine.⁴⁶ Quantitative assessment of the extent and evolution of ST depression is also diagnostically and prognostically important: in the core laboratory ECG analyses of 5199 NSTEMI-ACS patients from the Global Use of Strategies To Open occluded arteries (GUSTO) IIb trial, the sum of ST-segment depression in all leads showed a highly significant correlation with the prevalence of three-vessel or left main CAD and was a powerful independent predictor of 30-day mortality (Figure 2).⁵⁷ Slow recovery of extensive ST-segment depression, so-called 'acute circumferential subendocardial ischaemia',⁵⁸ following the cessation of symptoms may be a marker of sub-occlusive stenosis of a coronary artery supplying a large area of myocardium at risk (figure in [Supplementary data online, Appendix](#)): in this case, current guidelines recommend STEMI-like approach with immediate CAG.^{12,13} T wave inversions in the absence of ST-segment changes are frequently observed in subacute NSTEMI-ACS. Transient ST-segment elevation may be caused by unstable coronary thrombosis and/or coronary spasm and suggests early CAG for diagnosis, though without evidence of benefit as compared with a delayed approach.⁵⁹

ST-segment abnormalities may also be caused by non-ischaemic factors, such as pericarditis or left ventricular hypertrophy, highlighting the importance of total evidence from clinical history and presentation, ECG findings, and blood biomarkers.

Artificial intelligence models have been validated for diagnosis and risk prediction in ACS based on the 12-lead ECG, showing superior accuracy to detect acute coronary occlusion when compared with STEMI

criteria.⁶⁰⁻⁶³ These data suggest its potential to improve ACS triage, particularly in the pre-hospital setting and peripheral hospitals, ensuring appropriate and timely referral for immediate revascularization.

Impact of myocardial necrosis markers and the Universal Definition of Myocardial Infarction

The amount of myocardial damage is prognostically important across the ACS spectrum.^{64,65} Two evolutions have impacted on the diagnostic and epidemiological picture of NSTEMI, namely the Universal Definition of Myocardial Infarction (UDMI) and the development of hs-cTn assays.

In 2000, the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) published a position paper aimed at unifying the diagnosis of MI in both clinical trials and practice.⁶⁶ Three additional reports, based on subsequent clinical trials and observations, defined a new type resulting from an imbalance of myocardial oxygen demand and supply termed as T2MI.⁶⁷⁻⁶⁹ This was to distinguish this syndrome from a Type 1 MI resulting from thrombotic coronary arterial obstruction. Currently, the fifth definition is in progress and will be published in 2026. The key points of the fourth document are schematized in Figure 3. Non-ST-segment elevation myocardial infarction is a Type 1 MI resulting from the same pathophysiologic process as a STEMI, i.e. an atherosclerotic plaque rupture or erosion with subsequent thrombotic obstruction of the arterial lumen. Non-ST-segment elevation myocardial infarctions are usually associated with non-occlusive luminal obstruction of sufficient severity to result in myocardial necrosis, but can also be the result of total obstruction of an artery with sufficient collateral flow to minimize the ischaemic injury. Approximately 10% of patients with NSTEMI undergoing angiography show MINOCA.

Non-ST-segment elevation myocardial infarctions usually have less acute myocardial injury as compared with STEMI. Therefore, cTn levels are usually lower with NSTEMI, but due to the worse baseline characteristics, often with greater degrees of underlying atherosclerosis and older age, the slope of the relation between myocardial damage and adverse outcome is steeper in NSTEMI (Figure 4).^{64,70}

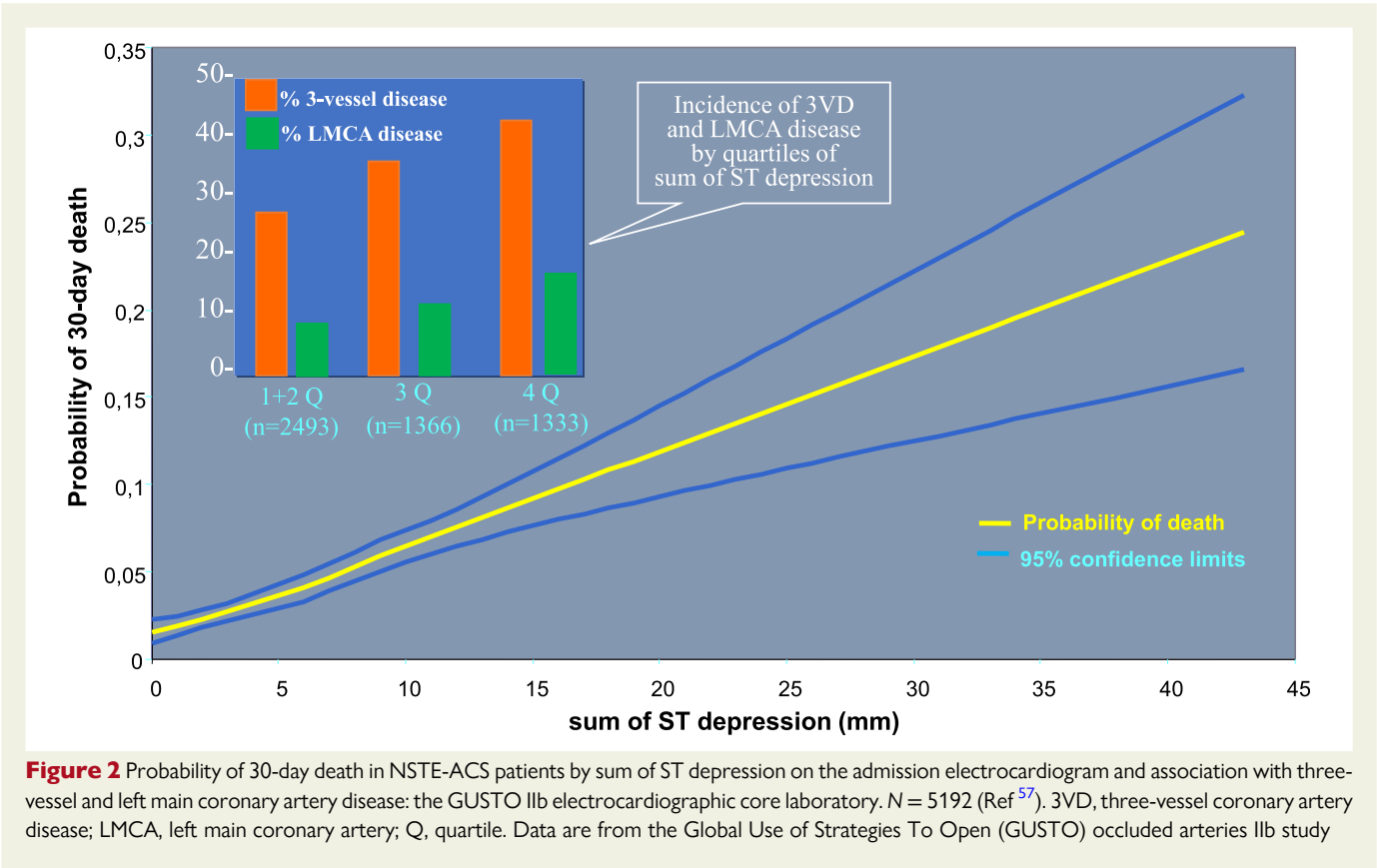


Figure 2 Probability of 30-day death in NSTE-ACS patients by sum of ST depression on the admission electrocardiogram and association with three-vessel and left main coronary artery disease: the GUSTO IIb electrocardiographic core laboratory. N = 5192 (Ref ⁵⁷). 3VD, three-vessel coronary artery disease; LMCA, left main coronary artery; Q, quartile. Data are from the Global Use of Strategies To Open (GUSTO) occluded arteries IIb study

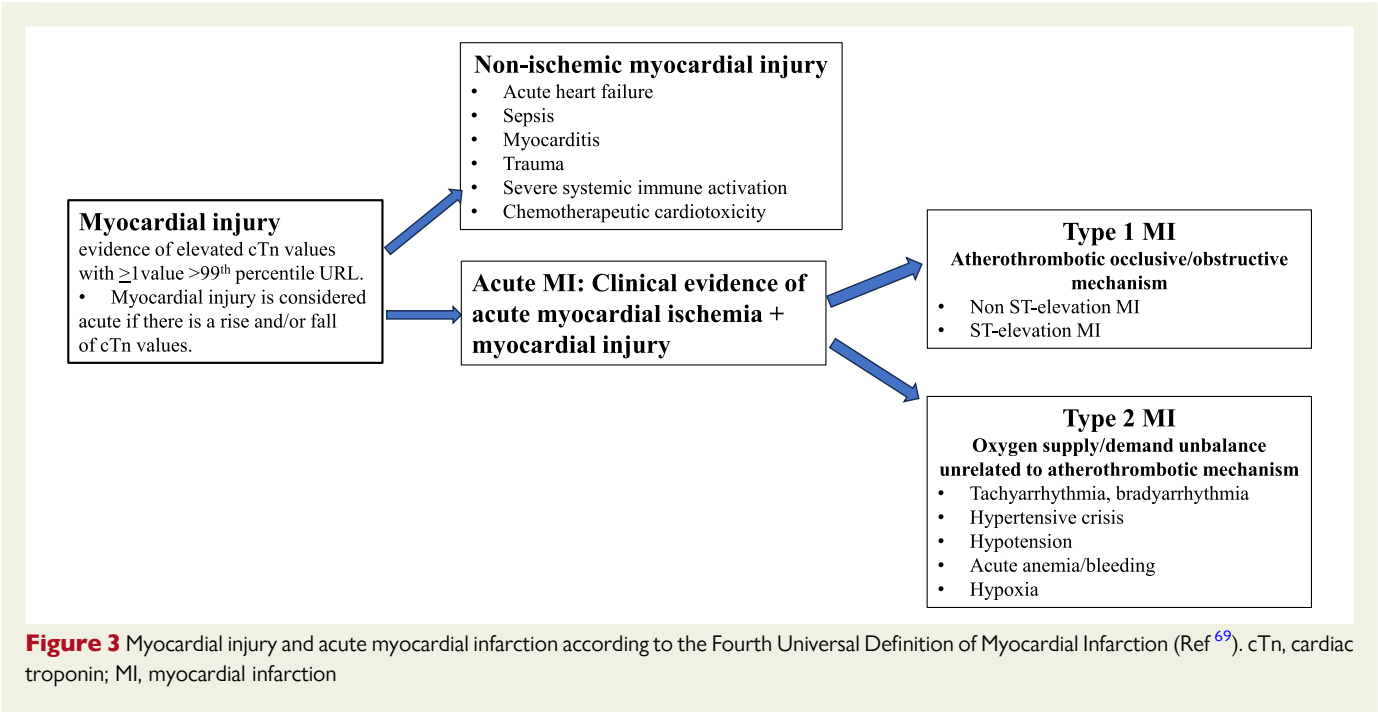
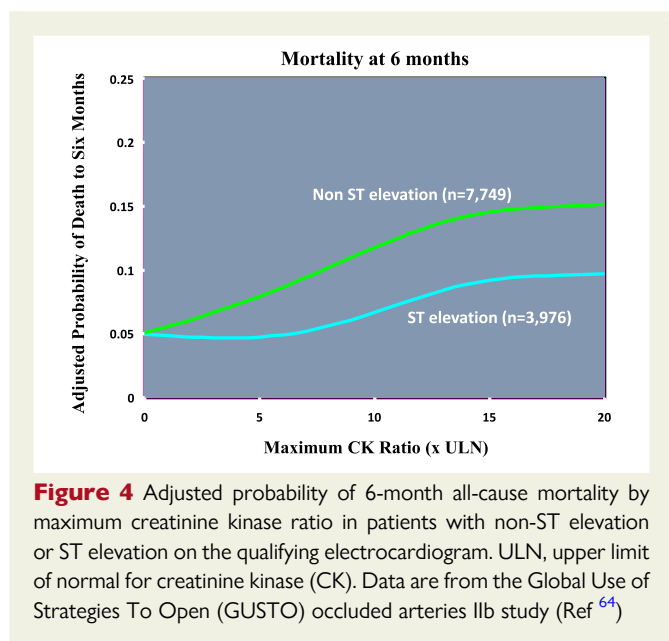


Figure 3 Myocardial injury and acute myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction (Ref ⁶⁹). cTn, cardiac troponin; MI, myocardial infarction

Not all myocardial injury is ischaemic in origin even though it results in elevated cTn levels, and this is termed non-ischaemic myocardial injury. For example, myocyte necrosis can arise from trauma, infection and inflammation, chemotherapeutic toxicity, and/or severe systemic

immune activation. Type 2 MI may occur in patients with tachyarrhythmia, severe hypertension, hypotension, hypoxaemia, anaemia, and many other situations involving critical illness.¹⁵ In each of these conditions, myocardial perfusion is not able to sustain myocyte viability with



the development of elevated hs-cTn levels. Myocardial injury that does not result from ischaemia should be classified as non-ischaemic myocardial injury, and the term 'infarction' should *not* be employed. Erroneous use of the term infarction for these patients led to a sudden increase in the population incidence of MI in public health statistics.⁷¹

The continuing refinement of hs-cTn assays has resulted in earlier detection/rule out of myocardial injury,^{12,13} accelerates decision-making, reduces emergency department overcrowding, and guides early initiation of therapy. Markers for plaque instability, as myeloperoxidase, myeloid-related protein 8/14, pregnancy-associated plasma protein-A, C-reactive protein, fms-like tyrosine kinase 1, and placental growth factor, have not been shown to add diagnostic value for acute MI. Other novel biomarkers such as FGF-23, mid-regional pro-adrenomedullin, mid-regional pro-atrial natriuretic peptide, and copeptin are being evaluated for possible future diagnostic or prognostic use. However, a limited understanding of their pathobiology and release mechanisms impairs their use currently.

The increased sensitivity of hs-cTn assays has included patients with previously undetectable myocardial necrosis in the NSTEMI population. This evolution has been associated with overdiagnosis of MI, particularly when testing is performed in patients without ischaemic symptoms and in older adults with aspecific presentation. Implementation of age-specific 99th percentiles might reduce overdiagnosis of abnormal Tn concentrations in older adults.^{72–74}

Thus, when describing trends in treatment and outcome of NSTEMI-ACS, with the increasing rates of revascularization procedures during the last 30 years, multivariable regression modelling has been used to suggest that the observed improvement in outcome in NSTEMI-ACS is due to more effective treatment rather than to a change in patient population.^{23–27} These trends have also been influenced by the fact that more patients with advanced age, frailty, and multimorbidity are being admitted to coronary care units and managed with an invasive approach.^{30,75–77} Future studies with the almost systematic use of CAG and revascularization should confirm whether, besides their undisputable diagnostic value, the acute ECG and laboratory findings maintain their powerful predictive value in NSTEMI-ACS.

Coronary angiography

Due to the above-mentioned complexity of NSTEMI-ACS and the causal role of coronary atherothrombosis, CAG is an essential part of the diagnosis and management of this syndrome. Randomized clinical trials comparing an invasive vs a conservative approach in NSTEMI-ACS randomized patients before CAG, an approach that precludes a complete diagnosis in this condition. However, both in registries and RCTs, only between 50% and 80% of patients undergoing CAG received revascularization,^{23–27,30,78,79} a fact that, in an intention-to-treat analysis, may have diluted any benefit of revascularization in patients with an angiography-based indication.

The indication for CAG in NSTEMI-ACS is twofold ([Graphical Abstract](#)):

1. To make a definitive differentiation between Type 1 MI and T2MI, which may not be straightforward without CAG. Type 2 MI patients tend to have more comorbidities and are often older and more frequently women.^{80,81} Moreover, even in T2MI, CAD may be present, often diffuse and involving multiple arteries. Although current evidence does not support routine revascularization in T2MI, CAG is recommended when the diagnosis remains uncertain.^{82,83}
2. To assess the possible indication for revascularization: this critical decision requires exclusion of patients with MINOCA or atherosclerotic disease not suitable for revascularization.

In most patients, CAG is limited to visual angiographic findings, but in some patients, additional imaging techniques may assist with establishing the final diagnosis ([Figure 5](#)). A recent consensus statement has highlighted the key role of intracoronary imaging techniques also for better understanding plaque morphology and vulnerability.⁸⁴ Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) aids in the identification of plaque rupture, erosion, and thrombosis, with impact on clinical decision-making. If no epicardial CAD is found, coronary physiology assessments and/or intravascular imaging may be useful for diagnosing different types of MINOCA.

In patients without evidence of myocardial ischaemia, computed tomographic coronary angiography (CTCA) may rule out significant CAD and identify other major life-threatening diagnoses, e.g. critical disease of the thoracic aorta or pulmonary embolism. Cardiac magnetic resonance (CMR) may be useful in identifying clinical conditions responsible for cTn elevation, such as myocarditis or specific cardiomyopathies, or to establish the real presence of myocardial necrosis.^{84,85}

Myocardial infarction with non-obstructive coronary arteries

In the fourth UDMI, MINOCA is defined as an MI with underlying non-obstructive CAD (no stenosis $\geq 50\%$) in any major epicardial vessel.⁶⁹ Thus, myocardial injury is excluded from MINOCA diagnosis. However, MINOCA is a working diagnosis with several possible mechanisms:^{12,86}

- (1) Clinically overlooked obstructive diseases (e.g. total occlusion of a small coronary artery subsegment resulting from plaque disruption or embolism, or an overlooked $\geq 50\%$ distal stenosis) need to be excluded.
- (2) Cardiac magnetic resonance has been shown to be of great value, with 77% of all MINOCA confirmed after exclusion of myocarditis and Takotsubo syndrome.^{87,88}
- (3) An important distinction is between atherosclerotic and non-atherosclerotic MINOCA: atherosclerosis-based MINOCA

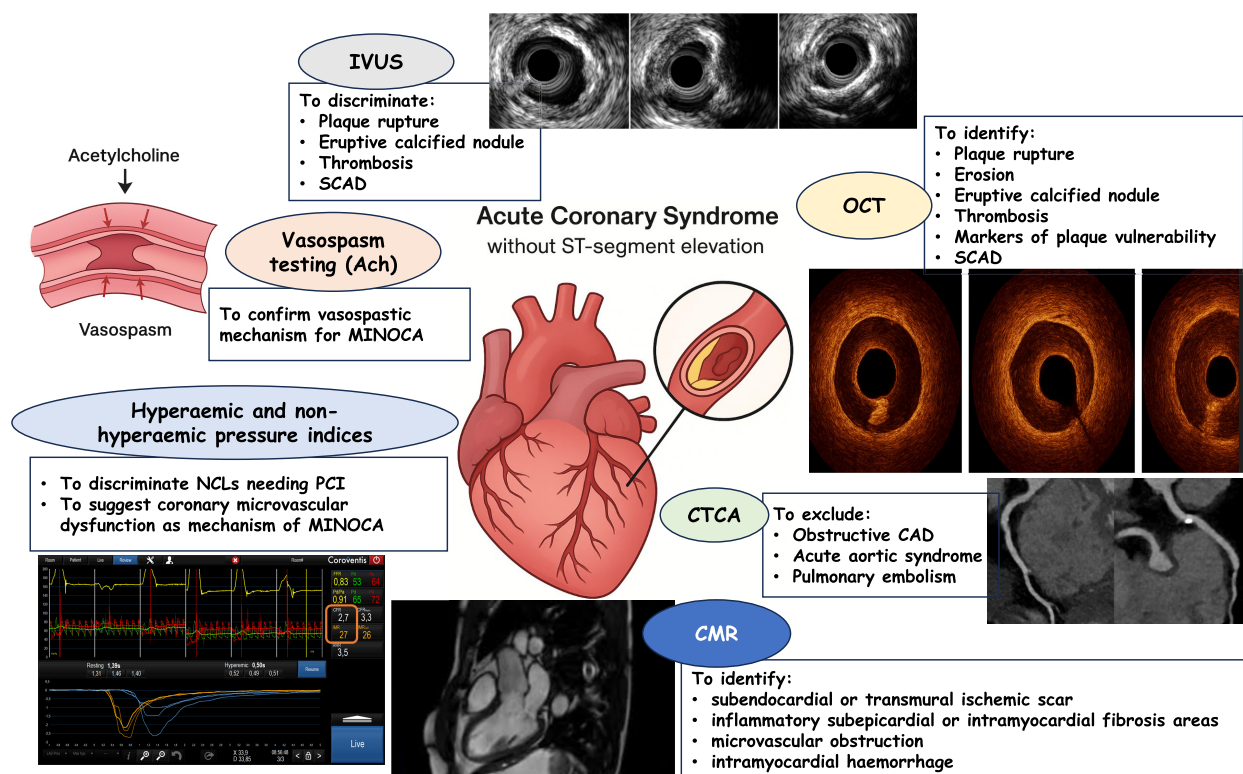


Figure 5 Information provided by additional imaging and physiology studies after coronary angiography in selected non-ST-segment elevation acute coronary syndrome cases (see text for explanations). Ach, acetylcholine; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CTCA, computed tomography coronary angiography; IVUS, intravascular ultrasound; MINOCA, myocardial infarction with non-obstructed coronary artery; NCLs, non-culprit lesions; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection

- portends a worse prognosis as compared with non-atherosclerosis-based MINOCA.⁸⁹ Approximately one-half of atherosclerosis-based MINOCAs are due to plaque rupture, erosion, or a calcified nodule, usually complicated by coronary thrombosis and distal embolization.⁹⁰ With plaque erosion, which according to *in vivo* intracoronary imaging studies causes up to 40% of ACS,⁸⁴ the loss of surface endothelium with the expression of high concentration of hyaluron and neutrophil accumulation may lead to thrombosis without obstructive CAD.⁹¹ Of note, a study combining CMR and OCT identified potential mechanisms in 85% of women with MINOCA, 76% of whom were ischaemic.⁹²
- (4) Intracoronary imaging may also help in the diagnosis of spontaneous coronary artery dissection at times overlooked during angiography. This condition may be responsible for as many as 25% of ACS cases in young women, may be associated with fibromuscular dysplasia in other vascular beds, and can be compounded by emotional stress, extreme physical activities, and sympathomimetic drugs.^{93,94}
 - (5) Among the non-atherosclerotic causes, coronary spasm has a prevalence of 6% among all AMIs.⁹⁵ Coronary epicardial spasm is more common than microvascular spasm as a cause of MINOCA and is associated with worse outcomes.⁹⁶ Hyper-reactivity of the smooth muscle cells involving the rho-kinase enzyme is the underlying mechanism.⁹⁷ Coronary provocation testing with acetylcholine has been shown to be safe even in an early phase after admission.⁹⁸

- (6) A myocardial bridge with epicardial spasm is also a possible cause of MINOCA.⁹⁹
- (7) Finally, subclinical MI has been shown in 10.8% of patients with patent foramen ovale undergoing CMR after a first cryptogenic cerebral ischaemic event.¹⁰⁰ Careful echocardiographic evaluation including transthoracic, transoesophageal, and bubble contrast is of paramount importance in such cases.

The presence of CAD in MINOCA is associated with a worse prognosis as compared with individuals with entirely normal coronary arteries.¹⁰¹ Although no specific evidence has been so far published for treatment-specific MINOCA subtypes, searching for the mechanism of MINOCA is essential for tailoring appropriate therapy as shown in [Table 2](#). The PROgnostic value of precision Medicine in patients with myocardial Infarction and non obStructive coronary artEries (PROMISE) randomized trial has shown the usefulness of personalized treatment in MINOCA to improve quality of life.¹⁰²

Routine invasive vs conservative strategy

Several RCTs^{103–107} and meta-analyses^{108,109} have provided strong evidence for early invasive management in high-risk patients, showing that routine CAG and, where indicated, coronary revascularization reduce the composite endpoint of death or MI. Major problems of these earlier

Table 2 Pathophysiology-tailored therapy of myocardial infarction with non-obstructive coronary arteries¹⁰²

Mechanism	First-line therapy
<u>Atherosclerotic</u>	
Plaque rupture/erosion	DAPT, statins ± PCI, or CABG beta-blockers and ACE inhibitors/ARB (with reduced EF)
<u>Non-atherosclerotic</u>	
Coronary artery spasm	Calcium channel blockers, nitrates, nicorandil, statins
Spontaneous coronary artery dissection	SAPT or DAPT, beta-blockers, ±PCI, or CABG for refractory ischaemia or haemodynamic instability
Coronary embolism	Treatment of the underlying condition (if possible), oral anticoagulation
Coronary microvascular dysfunction	Calcium channel blockers, beta-blockers, ACE inhibitors/ ARB, statins, nitrates, ranolazine

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; EF, ejection fraction; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

trials were the heterogeneity of included patients with different risk profiles and the high cross-over rates from conservative to invasive strategy. More recently, several RCTs investigated if the same benefit was consistent in older NSTEMI patients.^{30,110–112} Also in these studies, only between 50% and 62% of the patients in the routine invasive arm underwent revascularization. The largest SENIOR-RITA trial confirmed that a systematic invasive strategy in older patients does not affect long-term mortality, but reduced MI recurrences and the need for unplanned revascularization.⁷⁹ This result should not be minimized, because for older frail patients, avoiding repeated hospitalization can be as important as prognosis.¹¹³ Moreover, whereas subgroup analyses of the SENIOR-RITA trial did not show mortality benefit from an invasive approach in older patients with frailty or cognitive impairment,⁷⁹ a recent retrospective longitudinal analysis of England's national healthcare records found that cardiovascular causes are the principal mode of death in frail patients after an ACS, and revascularization is associated with short- and long-term survival benefits in people at intermediate and high risk of frailty (mostly NSTEMI-ACS) after adjustment for measured and unmeasured confounders.⁷⁶ Although these data should be interpreted with caution due to possible selection bias in providing revascularization,¹¹⁴ they suggest benefit from intervention even in frail elderly patients.

A major advance in terms of safety of the invasive approach has been the transition from the femoral to the radial artery access with significant reductions in major bleeding, acute kidney injury, and all-cause mortality.^{115,116} This approach is now being used in about 90% of the procedures also in older patients.⁷⁹ The increased use of an invasive approach to NSTEMI-ACS over the last three decades has been associated with a significant reduction in adjusted mortality rates in administrative datasets and national registries in Europe and the USA (Table 3).^{23–27,76}

Timing of invasive coronary angiography

Several modest-sized RCTs and meta-analyses have shown that an early (<24 h) invasive strategy does not substantially reduce the risk of mortality but, compared with a delayed strategy, reduces refractory angina in unselected NSTEMI-ACS patients.^{117–130} However, in high-risk patients, an early invasive strategy reduced major adverse cardiac events (MACEs).^{119,126} An individual patient data meta-analysis of eight RCTs including 5324 NSTEMI-ACS patients with a median follow-up of 180 days found a nonsignificant trend for mortality reduction in the early invasive group compared with the delayed invasive group {hazard ratio (HR) .81; [95% confidence interval (CI) .64–1.03]; *P* = .088}. However, lower mortality with an early invasive strategy was found in higher risk subgroups such as those with elevated cardiac biomarkers (HR .70; [.58–.99]), diabetes (HR .67; [.45–.99]), a GRACE risk score > 140 (HR .70; [.52–.95]), or aged ≥75 years (HR .65; [.46–.93]).⁷⁸ This meta-analysis was recently updated showing lower mortality.¹³¹ Two prominent, large, RCTs conducted 10 years apart were the primary contributors of these findings.^{120,126}

The Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial¹²⁰ randomized 3031 patients to an early (<24 h, median 14 h) or delayed (>36 h, median 50 h) invasive strategy. No significant benefit was observed for early invasive strategy for the primary endpoint of death, MI, or stroke at 6 months (9.6% vs 11.3%; HR .85; [.68–1.06]). However, a relative risk reduction of 28% was shown in the secondary outcomes of death, MI, or refractory ischaemia (9.5% vs 12.9%, HR .72; [.58–.89]). In a pre-specified subgroup analysis, patients with a GRACE risk score > 140 benefited from an early invasive strategy in terms of both primary (13.9% vs 21%; HR .65; [.48–.89]) and secondary endpoints (13.7% vs 21.6%; HR .62; [.45–.83]), with significant interaction *P* values.

The Very Early vs Deferred Invasive evaluation using Computerized Tomography (VERDICT) trial compared an early (median 4.7 h after diagnosis) to a delayed invasive strategy (median 61.6 h) among 2147 NSTEMI-ACS all-comers with an endpoint of MACE or admission for HF at a median follow-up of 4.3 years. Overall, there was no benefit with the early invasive strategy, but high-risk patients (GRACE score > 140) had a relative risk reduction of 19% in the early invasive strategy compared with the delayed invasive strategy (HR .81; [.67–1.00]). Fewer HF hospitalizations with the early invasive strategy were also reported (HR .78; [.60–1.01]).¹²⁶

Thus, the most prominent high-risk feature to guide the timing of CAG should be a GRACE risk score > 140. However, due to the lack of studies assessing the value of a GRACE risk score > 140 in guiding the timing of CAG and revascularization and inconsistent data on long-term outcomes, according to the current ESC and ACC/AHA guidelines, the GRACE risk score ‘should be considered’ for estimating prognosis and guiding an early invasive strategy < 24 h (Class IIa).^{12,13}

Studies have shown promise for artificial intelligence algorithms to provide probability scores for coronary occlusion in patients with NSTEMI.¹³² Whether this may allow more appropriate selection of NSTEMI patients who would benefit from immediate CAG should be studied.

Coronary revascularization in multivessel disease

It is not always easy to identify a culprit lesion in NSTEMI-ACS, as up to 30% of culprit lesions may be misdiagnosed or incorrectly identified.¹³³ In this condition, coronary imaging can be crucial. In particular, OCT is able to identify thrombus, erosion, and dissection to discriminate the

Table 3 Summary of selected administrative data (USA, UK)^{23,25} and national cardiology registries (Italy, France, Sweden)^{24,26,27} showing the evolution of invasive approach, revascularization rates during index admission, and mortality in non-ST-segment elevation acute coronary syndrome over the last three decades

Study	Years	Country	Numbers, mean age (y)	% invasive	% revascularization	Mortality	OR, HR
Khera S ²³ Nationwide Inpatient Sample	2002–11	USA	3 981 119 mean age 70	28→41	Not reported	Hospital death 5.5%→3.9%	Adj ^a OR [per year] .976; 95% CI, .974–.978; P < .001
De Luca L ²⁴ ANMCO registries	2001–10	Italy	4350 ≥ 75years mean age 81	27→68	10→52	30-day death 14.6%→6.2%	Adj ^a OR [2010 vs 2001] .34; 95% CI, .21–.56; P < .0001
Hall M ²⁵ Myocardial Ischaemia National Audit Project	2003–13	UK	389 057 median age 72	35→72	8→36	6-month death 10.8%→7.6%	Adj ^a HR [per year] .968; 95% CI, .966–.971
Puymrat E ²⁶ USIC, FAST-MI	1995–2015	France	5844 mean age 68	25→95	13→67	6-month death 17.2%→6.3%	Adj ^a HR [2015 vs 1995] .40; 95% CI, .30–.52
Szummar K ²⁷ SWEDEHEART	1994–2014	Sweden	205 693 mean age 74	1.9→73	6.5→58	1-year death 26.0%→14.8%	Adj ^a OR [per 2-year period] .930; 95% CI, .926–.935

OR, odds ratio; HR, hazard ratio.

^aAdjustment for covariates is different in the various studies.

culprit lesion/vessel. No specific RCTs have addressed the additional benefit of preventive revascularization of non-culprit lesions in multivessel disease. The principal information comes from observational studies and meta-analyses showing that complete revascularization may be associated with higher event rates during short-term follow-up but fewer repeat revascularizations and deaths at longer follow-up.^{134–136}

A pre-specified analysis of the Functional Assessment in Elderly MI Patients with Multivessel Disease (FIRE) trial¹³⁶ evaluated the effect of physiology-guided complete revascularization vs culprit-only PCI and showed that complete revascularization significantly reduced MACE in both NSTEMI and STEMI patients,²² a benefit persisting at 3-year follow-up.¹³⁷ The European guidelines, published before last evidence, recommended complete revascularization as Class IIa, while the most recent North-American guidelines upgraded complete revascularization to Class I.^{12,13} Both guidelines suggest as Class IIb coronary physiology for the discrimination of non-culprit lesions needing revascularization. The ongoing COMPLETE-NSTEMI trial is assessing the benefit of complete revascularization vs culprit lesion-only PCI in NSTEMI patients with identifiable culprit lesion and multivessel CAD (NCT05786131).¹³⁸

Drug therapy

The focus on drug therapy for NSTEMI-ACS is shifting from powerful and prolonged antiplatelet therapy (APT) to a more disease-modifying treatment. This change has been the consequence of improvements in PCI, increased revascularization rates with reduced risk of recurrent MI, awareness of the prognostic impact of bleeding, and the growing evidence favouring lipid-lowering therapy and new agents, such as the sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1ra), which reduce hospitalizations in patients with HF and renal dysfunction. As a matter of fact, after the acute phase, markers of HF and renal dysfunction are the most potent predictors of mortality at follow-up,^{139–143} and the risk for incident HF has been shown to be greater than recurrent MI, even among patients with normal EF.⁴⁸

Antiplatelet therapy

The relevant role of platelets in the pathogenesis of ACS^{143–145} supports the use of APT in the acute phase as well as to reduce the risk of recurrent MI and stent thrombosis.¹⁴⁶ In the seminal CURE trial,¹⁴⁷ dual antiplatelet therapy (DAPT) using aspirin and clopidogrel for a median of 9 months reduced the composite outcome of cardiovascular death, non-fatal MI, or stroke by 20% as compared with aspirin in NSTEMI-ACS patients, though with a 38% increase in major bleeding. The significant effect on MACE was due almost exclusively to reduced MI risk. Subsequent studies showed that MACE could be further reduced using more powerful P2Y₁₂ blockers,^{148–150} at the expense of a further 30% increase in major bleeding. Therefore, a patient-tailored assessment of ischaemic and bleeding risk should advise the decision about the type and duration of DAPT.

Two issues concerning DAPT in NSTEMI-ACS have been long debated, i.e. the timing of initiation in the acute phase and the duration of administration:

- (1) Although the protocols of the CURE trial,¹⁴⁷ in which only 21% of patients underwent PCI a median of 10 days after randomization, and of the PLATO trial¹⁵⁰ required DAPT initiation before CAG, directing guidelines towards DAPT initiation upstream of CAG, subsequent randomized and observational studies with shorter

delay to PCI showed that such a strategy does not reduce MACE, but increases major bleeding.^{151–155} Current European guidelines have issued a Class IIIA recommendation against upstream DAPT in NSTEMI-ACS, while the ACC/AHA guidelines simply state that upstream DAPT is reasonable if the expected time to CAG is >24 h (Class IIb).^{12,13} In P2Y₁₂ receptor inhibitor-naïve patients, especially when oral administration is not feasible in the setting of emergent PCI, i.v. use of cangrelor may be considered on a case-by-case basis.^{12,156}

- (2) The second issue was the duration of 'mandatory DAPT' after ACS. The awareness that bleeding may negatively impact on mortality^{157,158} mitigated in the ESC guidelines the indication for 12-month DAPT by adding the sentence 'unless there is a high bleeding risk'.¹² However, in contemporary studies and meta-analyses, de-escalation strategies by abbreviating aspirin while continuing a P2Y₁₂ inhibitor, particularly ticagrelor, have shown net benefit over 12-month DAPT, regardless of their ischaemic or bleeding risks.^{159,160} Among the bleeding reduction strategies, the 2025 North-American Guidelines recommend (Class IA) transition to ticagrelor monotherapy 1 month post-PCI in patients who have tolerated DAPT with ticagrelor.¹³ Alternative 'de-escalation' strategies (i.e. switching from ticagrelor or prasugrel to clopidogrel) may be considered to reduce bleeding risk, although the safety with regard to risk of MACE is less firmly established (Class IIb recommendations in both guidelines).^{12,13} Whether the standard of 12-month DAPT will be replaced by the de-escalation strategies or will persist,^{161,162} at least in patients at high ischaemic risk,^{161–163} will be informed by future studies.

For long-term treatment, single APT, either aspirin or clopidogrel, is generally recommended. A recent RCT¹⁶⁴ and a meta-analysis of seven RCTs comparing aspirin and clopidogrel including 28 982 patients with a median follow-up of 2–3 years showed superiority of clopidogrel over aspirin monotherapy for major adverse cardiovascular and cerebrovascular events prevention with no difference in bleeding.¹⁶⁵

Secondary prevention strategies

Most NSTEMI-ACS patients have multiple risk factors, extensive CAD, and multimorbidity. Current guidelines recommend (Class IA) a comprehensive and multidisciplinary exercise-based rehabilitation and prevention programme to promote a healthy lifestyle by controlling cardiovascular risk factors, including dietary advice, tobacco counselling, and physical activity assistance with prescription of exercise training.^{13,80} This recommendation is reinforced by the results of a contemporary RCT showing that a multidomain rehabilitation intervention in older patients (median age 80 years) with AMI and impaired physical performance resulted in a lower incidence of cardiovascular death or unplanned cardiovascular hospitalization within 1 year than usual care.¹⁶⁶ A healthy diet, particularly a Mediterranean-style diet, can reduce cardiovascular risk through improvement in glucose and lipid metabolism, enhanced endothelial function, and reduction of neutrophil count,¹⁶⁷ potentially slowing the progression of atherosclerosis.¹⁶⁸

Lipid-lowering drugs represent a mainstay of secondary prevention. The treatment goal is to reduce LDL cholesterol to <55 mg/dL and achieving a ≥50% reduction from baseline¹² with a lower target (<40 mg/dL) for patients who experience a second cardiovascular event within 2 years. If these goals are not reached with high-intensity statin, ezetimibe added during the ACS hospitalization has been associated with reduced risk of MACE as compared with late combination

therapy,¹⁶⁹ whereas proprotein convertase subtilisin/Kexin type 9 inhibitors are recommended in patients who do not achieve their LDL-C goal despite maximum tolerated statin and ezetimibe therapy.¹²

The introduction of SGLT2i after an AMI is recommended (Class IA) in patients with Type 2 diabetes (T2DM).³⁶ There are no data to support the routine use of SGLT2i in patients with recent MI without diabetes, even in the presence of left ventricular dysfunction, following the neutral results of dedicated trials.^{170,171} Current recommendations for the use of GLP1ra also include only patients with T2DM. In high-risk patients with T2DM, oral semaglutide reduced MACE independently of concomitant SGLT2i treatment, and this combination appears to be safe.^{172,173} Moreover, semaglutide has a Class IIa recommendation in overweight or obese patients without T2DM with ascertained cardiovascular disease to reduce MACE.³⁶

Patients with chronic kidney disease, especially with albuminuria, with or without cardiovascular disease and/or diabetes, derive renal and cardiovascular benefit from SGLT2i.^{174,175}

Finally, the long-term use of colchicine appears questionable in light of the recently reported negative results of the CLEAR trial showing no benefit from colchicine vs placebo when administered soon after AMI, despite a significant reduction in C-reactive protein.¹⁷⁶ Other anti-inflammatory agents, including interleukin-6 inhibitors, are currently under investigation in large-scale trials.¹⁷⁷

Conclusion

Non-ST-segment elevation ACS encompasses a wide spectrum of clinical and pathophysiological presentations of coronary atherothrombosis whose diagnosis and treatment require assessment for spontaneous myocardial ischaemia, myocyte damage, and various degrees of CAD. Initial diagnosis and risk stratification have been shown to be reliably determined by typical symptoms, ECG changes, and hs-cTn elevation. Timely CAG should no longer be considered one of the possible strategic options in NSTE-ACS, but rather a key component of the initial diagnostic evaluation to exclude other ischaemic or non-ischaemic conditions with similar clinical presentation and to guide revascularization in patients with critical CAD. The safety of this approach has been shown even in fragile and multimorbid patients. Post-acute treatment should be focused on disease-modifying approaches and patient-tailored antithrombotic therapy.

Supplementary data

Supplementary data are available at [European Heart Journal](https://www.eurheartj/advance-article/doi/10.1093/eurheartj/ehaf326) online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for this manuscript.

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